REMARKS

In view of the foregoing amendments and the following representations, reconsideration and allowance of the above-identified application is respectfully requested.

Claims 1, 9-10, 12-16 and 34-35 are pending in the present application.

On page 2 of the Office Action, the Examiner objected to claim 8 for failing to further limit the previous claim. In response to this rejection, Applicants have canceled claim 8 without prejudice.

On page 3 of the Office Action, the Examiner rejected claims 10, 12, 13 and14 under 35 U.S.C. § 112, second paragraph, because the term "first enteric coating agent" lacked an antecedent basis. The Examiner also objected to claim 12 because of improper grammar. In response to these rejections and objection, Applicants have amended claims 1, 9-10 and 12-16 to provide proper antecedent basis and to correct inadvertent grammatical errors. No new matter is added by these amendments. Support can be found on page 6, line 7 to page 7, line 11 of the specification as filed.

Applicants have also added new claims 34 and 35. No new matter is added by these new claims. Support can be found in the claims as originally filed; page 4, lines 20-21 (opioid amount); page 4, line 24 to page 5, line 9 (gel or swelling binder and amounts); page 6, line 25 to page 7, line 11 (pH dependent material descriptions); and Examples 1 and 2 of the specification as filed.

On pages 4-11 of the Office Action, the Examiner rejected claims 1, 7-17 and 20-24 under 35 U.S.C. § 103(a) as being unpatentable over Mazer et al., United States Patent No. 5,160,742 (hereinafter "Mazer") in view of Saslawski et al., United States Patent No. 6,372,255 (hereinafter "Saslawski") and further in view of Sackler et al., United States

Patent No. 5,478,577 (hereinafter "Sackler") and Jain et al., United States Patent No. 4,610,870 (hereinafter "Jain").

In response to this rejection, Applicants have amended the claims to recite a specific embodiment of the present invention. The current pending claims recite a sustained release oral tablet that consists of three essential structural elements: 1) an oxycodone core; 2) a single delayed release coating surrounding the core; and 3) an immediate release oxycodone coating surrounding the delayed release coating. The claimed tablet may also optionally consist of a final aesthetic or cosmetic coating. This final coating is optional and does not affect the *in vivo* or *in vitro* properties of the claimed dosage form.

Applicants have also amended the claims to specifically indicate that the oxycodone core must employ a high viscosity binder that gel or swells in the presence of water and the delayed release coating must employ a combination of two pH dependent materials where the first pH dependent material dissolves in a pH between 5 and 7 and the second pH material dissolves at a pH greater than 8. Applicants have further amended the claims to indicate that the delayed release coating employs a substantial portion of specific non-polymeric water insoluble processing aids.

Applicants have discovered that the unique combination of the recited water insoluble processing aids and two different pH dependent coating materials combined with the use of a hydrogel polymeric binder in the core, provides a safe and stable, sustained release oxycodone tablet.

None of the references alone or combined disclose or suggest to a skilled artisan the sustained release tablet recited in the pending claims.

Mazer, the primary reference relied upon by the Examiner, teaches dosage forms that contain multiple beads or pellets wherein the beads or pellets are coated with at least two different coatings. One of the multiple coatings may be zein and the other coating may comprise enteric polymers. Col. 6, lines 6-65. The Examiner admits Mazer fails to disclose a single coating and fails to disclose oxycodone as a possible drug. The Examiner also admits that Mazer fails to disclose an immediate release oxycodone layer. In addition to these major deficiencies, Mazer only describes dosage forms employing a plurality of multiple coated pellets, not a single coated tablet as required by the pending claims. Mazer also fails to disclose an oxycodone core that employs a high viscosity hydrogel binder as required by the pending claims.

The Examiner seeks to correct these major deficiencies in Mazer by improperly picking and choosing the missing elements from a number of secondary and tertiary references which do not provide any motivation or direction for selecting the specific teaching and combining it with Mazer.

The Examiner relies upon the secondary reference, Saslawski, for the motivation to further modify the Mazer dosage form to include an immediate release drug layer. The Examiner then relies upon the tertiary references, Sackler for the disclosure of oxycodone and Jain for the disclosure of high viscosity binders.

Applicants respectfully traverse this improper selection of elements from the numerous references.

First, there is no reason why a skilled artisan would combine the multiple coatings of Mazer into a single coating as required by the pending claims. The Examiner merely selects certain enteric polymers from the numerous coating materials disclosed in Mazer and

combines them into a single coating based upon the general statements in Mazer that indicate each coating has different dissolution properties when applied separately. Applicants do not dispute that Mazer teaches individual coatings have different dissolution properties, however, this general statement does not provide guidance or direction for selecting the various ingredients recited in the pending claims. More importantly, this general teaching in Mazer provides no guidance or motivation for selecting the specific combination of materials recited in the pending claims and consolidating them into a single coating which will necessarily exhibit different dissolution properties than the individual coatings taught by Mazer to control the release of oxycodone from a hydrogel core.

Second, Mazer provides no teaching or suggestion for employing a high viscosity hydrogel binder in the oxycodone core to further control the release of the oxycodone from the dosage form. The Examiner contends Mazer teaches the use of osomopolymers as recited in the pending claims because Mazer discloses polyvinylpyrrolidone on Col. 7, lines 15-30. Applicants respectfully disagree with this contention. Attached hereto as Exhibit A is the monograph for poylvinylpyrrolidone from the *Handbook of Pharmaceutical Excipients*, 4th ed. This monograph indicates that viscosity of the commercially available grades of polyvinylpyrrolodine at 10% concentration ranges from about 1 mPa s to 700 mPa s. *See* Exhibit A at p. 509 (Table IV). This viscosity for polyvinylpyrrolidone is well below the 50,000 mPa required by the pending claims.

Next, the Examiner contends that a skilled artisan would combine Mazer with Saslawski to arrive at the presently claimed dosage form because Saslawski discloses an immediate release drug layer. The Examiner admits that Saslawski does not mention oxycodone. Because neither Mazer nor Saslawski disclose oxycodone, Applicants

respectfully disagree with the Examiner's contention that a skilled artisan would look to these two references to arrive at the presently claimed sustained release oxycodone tablet and, more importantly, would be motivated to further modify the multi coating pellet teaching of Mazer to arrive at the presently claimed invention.

Finally, the Examiner contends that the tertiary references, Sackler and Jain, overcome any remaining deficiencies with Mazer and Saslawski. Applicants respectfully disagree with this contention. Applicants admit that Sackler discloses oxycodone, however, the disclosure is only in a laundry list of potential opioids. See Col.6, line 62 to Col. 7, lines 20. There is no specific guidance or teachings provided in Sackler for preparing a sustained release oxycodone tablet. In addition, there is no general or specific guidance provided by Sackler that would motivate a skilled artisan to select certain elements of Mazer and Saslawski and combine the selected elements with oxycodone to produce the sustained release tablet recited in the pending claims.

The addition of the Jain reference to Mazer, Saslawski and Sackler also fails to suggest to a skilled artisan the sustained release tablet recited in the pending claims. Specifically, Applicants respectfully submit there is no general or specific motivation provided in Jain that would motivate a skilled artisan to combine Jain with the cited references and modify the teachings of the primary and secondary references to arrive at the presently claimed invention. Jain fails to indicate that dosage forms disclosed in Jain could be used with oxycodone or even opioids. Further, the dosage forms disclosed in Jain require a coating that is "a combination of water-insoluble film former and water soluble film-former". Jain Col. 3, 41-45. Jain defines the water insoluble film formers at Col. 6, lines 53-63 and water soluble film formers at Col. 6, lines 47-52. At best, the addition of Jain to the

primary and secondary references would result in dosage form with a coating that comprises a water insoluble film forming polymer and an enteric polymer. This coating is not the coating recited in the present invention which employs two enteric materials and a substantial quantity of non polymeric, non-film forming water insoluble processing aids.

It is respectfully submitted that the pending claims are patentable over the cited references because there is no motivation to combine the references as suggested by the Examiner because primary and secondary references do not even disclose oxycodone. If the skilled artisan were to combine the cited references, there is no guidance or teaching in any of the cited references that would suggest to the skilled artisan a reason to neglect the multiple coating teaching of Mazer and modify the Mazer core and coatings by selecting isolated elements from Saslawski, Sackler and Jain to arrive at the presently claimed sustained release oxycodone dosage form, other than improper hindsight.

Based upon the foregoing amendments and representations, Applicants respectfully submit that the rejection of the claims in the above-identified application has been overcome and should be withdrawn. Early and favorable action is earnestly solicited.

Respectfully submitted,

/matthew j. solow/

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EXHIBIT A

Handbook of Pharmaceutical Excipients

FOURTH EDITION

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RS201.E87H36 2003
615'.19–dc21

2003002641

Povidone

1 Nonproprietary Names

BP: Povidone
JP: Povidone
PhEur: Povidonum
USP: Povidone

2 Synonyms

E1201; *Kollidon*; *Plasdone*; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2- pyrrolidinone polymer.

3 Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4 Empirical Formula — Molecular Weight

$(C_6H_9NO)_n$ — 2500–3 000 000

The USP 25 describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a *K*-value, ranging from 10 to 120. The *K*-value is calculated using Fikentscher's equation:[1]

$$\log z = c\left(\frac{75k^2}{1+1.5kc}\right)+k$$

where z is the relative viscosity of the solution of concentration c, k is the *K*-value $\times\ 10^{-3}$, and c is the concentration in % w/v.

Alternatively, the *K*-value may be determined from the following equation:

$$K\text{-value}\ \sqrt{\frac{300c\log z(c+1.5c\log z)^2+1.5}{0.15c+0.003c^2}}$$

where z is the relative viscosity of the solution of concentration c, k is the *K*-value $\times\ 10^{-3}$, and c is the concentration in % w/v.

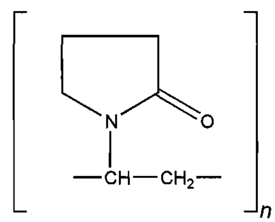
Approximate molecular weights for different povidone grades are shown in Table I.

Table I: Approximate molecular weights for different grades of povidone.

K-value	Approximate molecular weight
12	2 500
15	8 000
17	10 000
25	30 000
30	50 000
60	400 000
90	1 000 000
120	3 000 000

See also Section 8.

5 Structural Formula



6 Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes.[2,3] Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.[4–6] Povidone solutions may also be used as coating agents.

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone. *See* Table II.

Special grades of pyrogen-free povidone are available and have been used in parenteral formulations; *see* Section 14.

Table II: Uses of povidone.

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5–5

8 Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with *K*-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher *K*-value povidones are manufactured by drum drying and occur as plates.

9 Pharmacopeial Specifications

See Table III.

Table III: Pharmacopeial specifications for povidone.

Test	JP 2001	PhEur 2002 (Suppl 4.3)	USP 25
Identification	+	+	+
Characters	—	+	—
pH	—	—	3.0–7.0
$K \leqslant 30$	3.0–5.0	3.0–5.0	—
$K > 30$	4.0–7.0	4.0–7.0	—
Appearance of solution	+	+	—
Viscosity	—	+	—
Water	≤5.0%	≤5.0%	≤5.0%
Residue on ignition	≤0.1%	≤0.1%	≤0.1%
Lead	—	—	≤10 ppm
Aldehydes	≤500 ppm[a]	≤500 ppm[a]	≤0.05%
Hydrazine	≤1 ppm	≤1 ppm	≤1 ppm
Vinylpyrrolidinone	≤10 ppm	≤10 ppm	≤0.2%
Peroxides	≤400 ppm[b]	≤400 ppm[b]	—
K-value	25–90	—	10–120
≤15	90.0–108.0%	85.0–115.0%	85.0–115.0%
>15	90.0–108.0%	90.0–108.0%	90.0–108.0%
Heavy metals	≤10 ppm	≤10 ppm	—
Assay (nitrogen content)	11.5–12.8%	11.5–12.8%	11.5–12.8%

[a] Expressed as acetaldehyde.
[b] Expressed as hydrogen peroxide.

10 Typical Properties

Acidity/alkalinity: pH = 3.0–7.0 (5% w/v aqueous solution).
Density (bulk): 0.29–0.39 g/cm^3 for *Plasdone*.
Density (tapped): 0.39–0.54 g/cm^3 for *Plasdone*.
Density (true): 1.180 g/cm^3
Flowability:
20 g/s for povidone K-15
16 g/s for povidone K-29/32
Melting point: softens at 150°C.
Moisture content: povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities. *See* Figures 1 and 2.

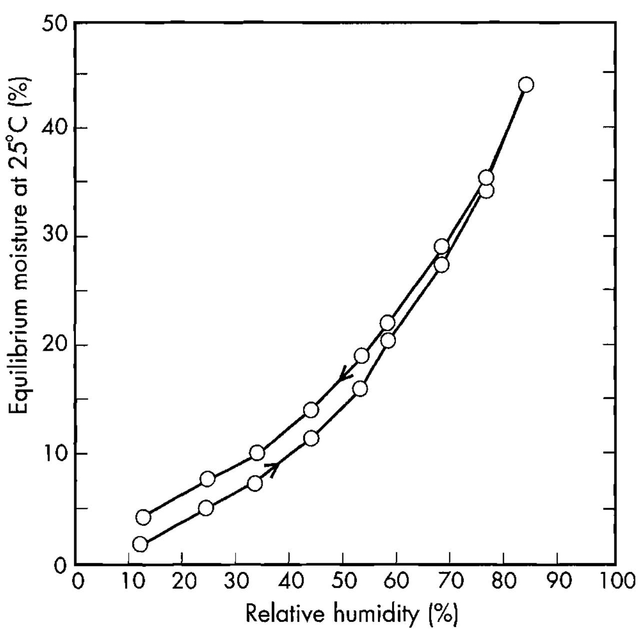


Figure 1: Sorption–desorption isotherm of povidone K-15 (*Plasdone K-15*).

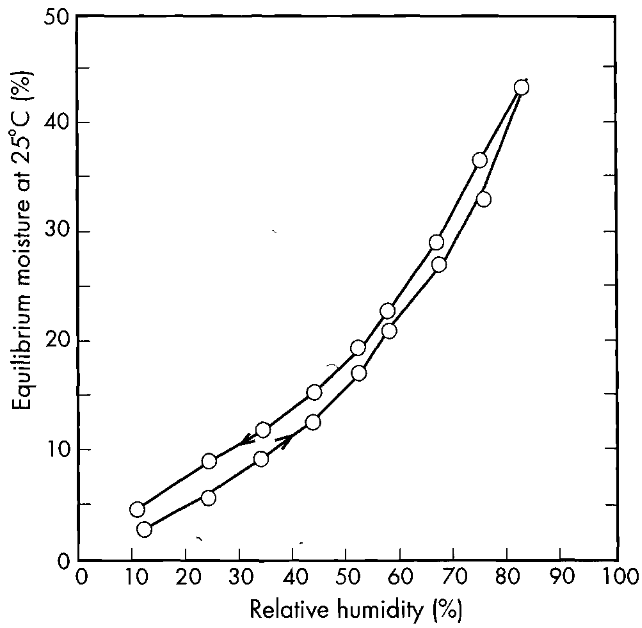


Figure 2: Sorption–desorption isotherm of povidone K-29/32 (*Plasdone K-29/32*).

Particle size distribution:
Kollidon 25/30: 90% >50 μm, 50% >100 μm, 5% >200 μm
Kollidon 90: 90% >200 μm, 95% >250 μm[7]

Solubility: freely soluble in acids, chloroform, ethanol, ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the *K*-value.

Viscosity (dynamic): the viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed. *See* Tables IV and V.[7]

Table IV: Dynamic viscosity of 10% w/v aqueous povidone (*Kollidon*) solutions at 20°C.[7]

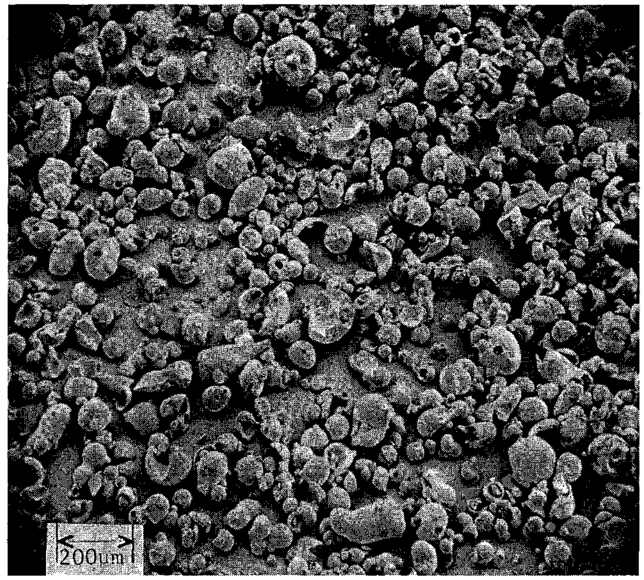
Grade	Dynamic viscosity (mPa s)
K-11/14	1.3–2.3
K-16/18	1.5–3.5
K-24/27	3.5–5.5
K-28/32	5.5–8.5
K-85/95	300–700

Table V: Dynamic viscosity of 5% w/v povidone (*Kollidon*) solutions in ethanol and propan-2-ol at 25°C.[7]

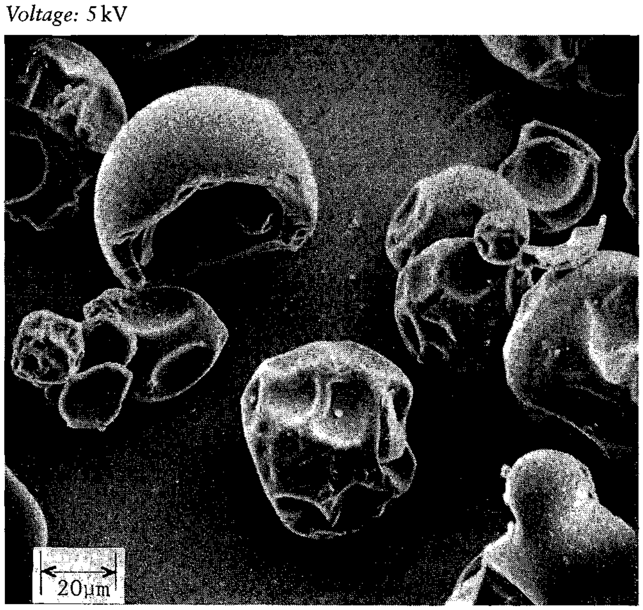
Grade	Dynamic viscosity (mPa s)	
	Ethanol	Propan-2-ol
K-12PF	1.4	2.7
K-17PF	1.9	3.1
K-25	2.7	4.7
K-30	3.4	5.8
K-90	53.0	90.0

SEM: 1
Excipient: Povidone K-15 (*Plasdone K-15*)
Manufacturer: ISP
Lot No.: 82A-1
Magnification: 60 ×
Voltage: 5 kV

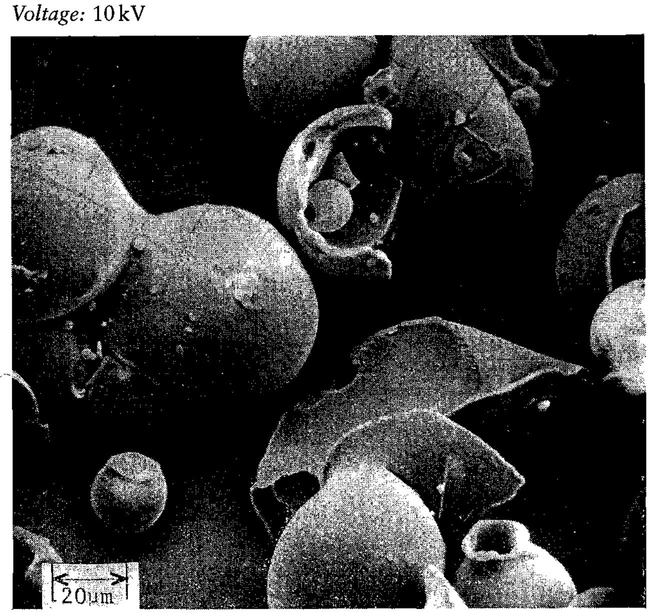
SEM: 3
Excipient: Povidone K-26/28 (*Plasdone K-26/28*)
Manufacturer: ISP
Lot No.: 82A-2
Magnification: 60 ×
Voltage: 5 kV



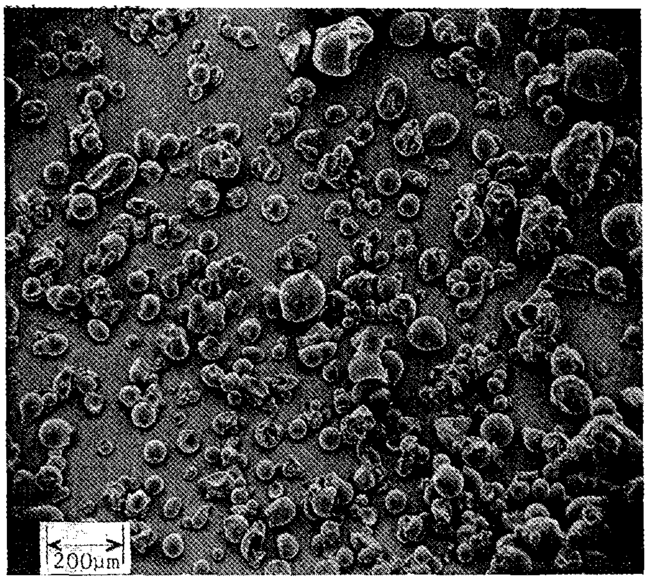
SEM: 2
Excipient: Povidone K-15 (*Plasdone K-15*)
Manufacturer: ISP
Lot No.: 82A-1
Magnification: 600 ×
Voltage: 5 kV



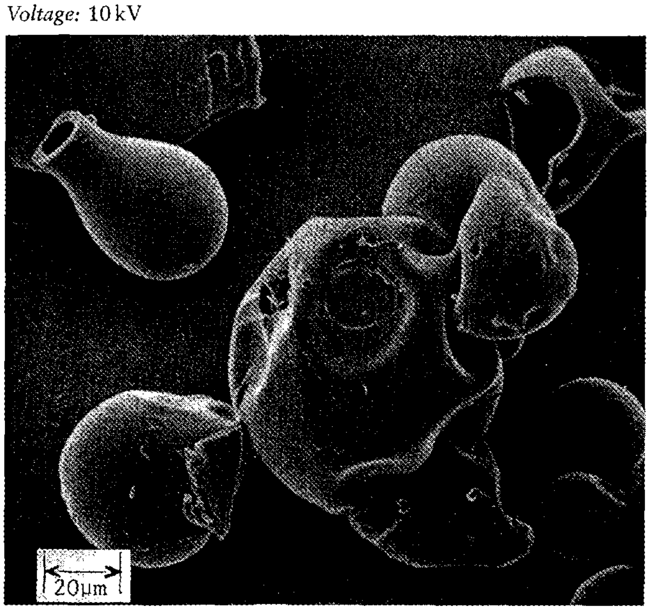
SEM: 4
Excipient: Povidone K-26/28 (*Plasdone K-26/28*)
Manufacturer: ISP
Lot No.: 82A-2
Magnification: 600 ×
Voltage: 10 kV



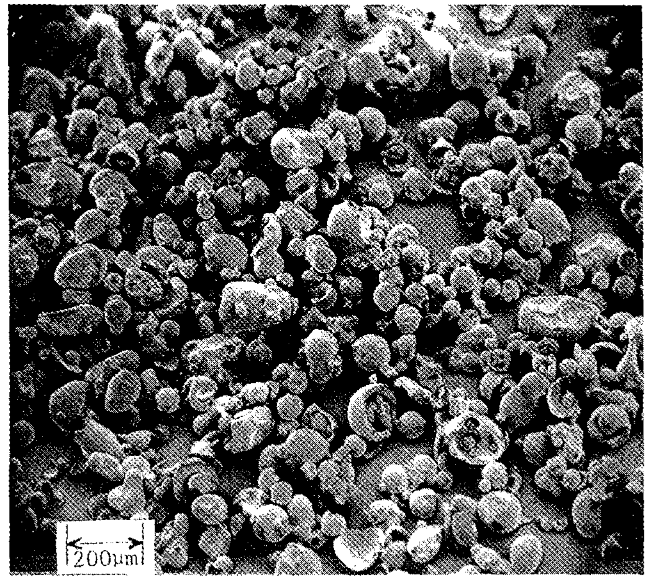
SEM: 5
Excipient: Povidone K-30 (*Plasdone K-30*)
Manufacturer: ISP
Lot No.: 82A-4
Magnification: 60 ×



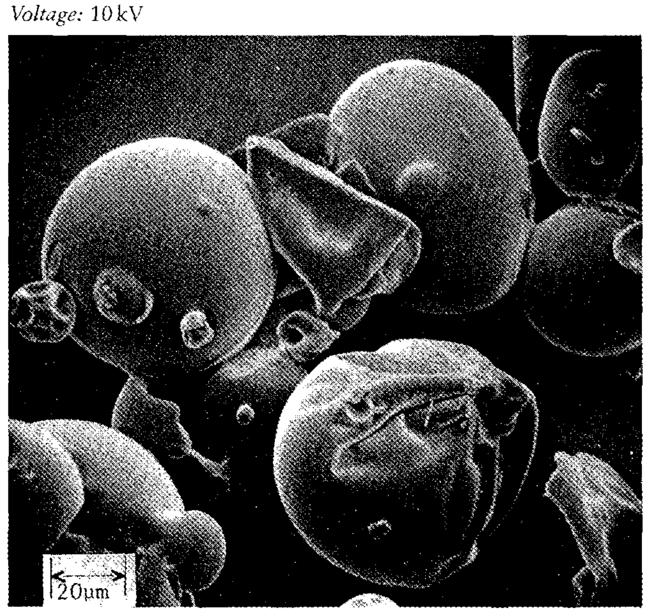
SEM: 6
Excipient: Povidone K-30 (*Plasdone K-30*)
Manufacturer: ISP
Lot No.: 82A-4
Magnification: 600 ×
Voltage: 10 kV



SEM: 7
Excipient: Povidone K-29/32 (*Plasdone K-29/32*)
Manufacturer: ISP
Lot No.: 82A-3
Magnification: 60 ×
Voltage: 5 kV



SEM: 8
Excipient: Povidone K-29/32 (*Plasdone K-29/32*)
Manufacturer: ISP
Lot No.: 82A-3
Magnification: 600 ×
Voltage: 10 kV



11 Stability and Storage Conditions

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties. Aqueous

solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds; *see* Section 18. The efficacy of some preservatives, e.g., thimerosal, may be adversely affected by the formation of complexes with povidone.

13 Method of Manufacture

Povidone is manufactured by the Reppe process. Acetylene and formaldehyde are reacted in the presence of a highly active copper acetylide catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer, vinylpyrrolidone, is then polymerized in the presence of a combination of catalysts to produce povidone.

14 Safety

Povidone has been used in pharmaceutical formulations for many years, being first used in the 1940s as a plasma expander, although it has now been superseded for this purpose by dextran.[8]

Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes.[8] Povidone additionally has no irritant effect on the skin and causes no sensitization.

Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site of intramuscular injections formulated with povidone.[9] Evidence also exists that povidone may accumulate in the organs of the body following intramuscular injection.[10]

A temporary acceptable daily intake for povidone has been set by the WHO at up to 25 mg/kg body-weight.[11]

LD_{50} (mouse, IP): 12 g/kg[12]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Accepted in Europe as a food additive. Included in the FDA Inactive Ingredients Guide (IM and IV injections; ophthalmic preparations; oral capsules, drops, granules, suspensions, and tablets; sublingual tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Crospovidone.

18 Comments

The molecular adduct formation properties of povidone may be used advantageously in solutions, slow-release solid-dosage forms, and parenteral formulations. Perhaps the best-known example of povidone complex formation is povidone–iodine, which is used as a topical disinfectant.

For accurate standardization of solutions, the water content of the solid povidone must be determined before use and taken into account for any calculations.

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